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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/273,217	Applicant(s) XIN-YUN HUANG
	Examiner Nirmal. S. Basi	Group Art Unit 1646

☒ Responsive to communication(s) filed on *Dec 22, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-35* is/are pending in the application.

Of the above, claim(s) *10-18 and 28-35* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-9 and 19-27* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-35* are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *1, 7*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Preliminary Amendment filed 12/22/00 has been entered.

Election/Restriction

2. Applicant's election with traverse of Group I (Claims 1-9), in Paper No. 12 (12/22/00), is acknowledged. The traversal is on the ground(s) that, "the four groups of invention identified in the outstanding office action are closely related and , therefore, would require common areas of search and consideration. Thus, there is no benefit in having these groups of claims examined and prosecuted in separate applications". This is found persuasive in part. Groups I and III, claims 1-9 and 19-27, are recombined as a result of Applicants amendment of claim 1 and will be examined. Group I as amended, reads on a method of identifying an ion channel blocker for an ion channel comprising providing an ion channel having an external vestibule portion, and Group III reads on a method of screening a drug for effectiveness as an ion channel blocker for an ion channel wherein the ion channel has an external vestibule portion. The inventions of groups II and IV are distinct for reasons of record, see paper number 10, 6/20/00. An examination of the materially different, patentably distinct inventions in a single application would constitute a serious undue burden on the examiner. The requirement is still deemed proper and is therefore made FINAL.

Claim Rejection, 35 U.S.C. 112, second paragraph

3. Claim 1-9 and 19-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 19 are indefinite because the name "external vestibule portion" has not been defined in the claims and specification so as to allow the metes and bounds of the claims to be determined. The specification discloses, "Most preferably, the external vestibule portion is located between the S5 transmembrane and the pore forming region of the channel protein or between the pore". The specification also discloses, "The vestibule portions of the ion channel listed herein include sequences which are substantially the same as the sequences listed herein. Variations, may be made, for example, the deletions or addition of amino acids that have minimal influence on the properties, structure, or nature of the amino acid", page 11, second paragraph. The term "external vestibule portion" has been defined only in general terms and is not clear if it encompasses portions of amino acid sequence outside the S5 transmembrane and the pore forming region of the channel protein, what particular amino acids determine it to being a "external vestibule portion", when is sequence "substantially the same as the sequences listed herein" as compared to when it is not "substantially the same as the sequences listed herein", what is the "minimal influence" that can be exerted and what property does it apply to, so as to allow the metes and bounds of the claims to be determined. Therefore, name "external vestibule portion" does not sufficiently serve to characterize said portion or the channel protein it encompasses.

Claim 1 is indefinite because it is not clear if the antibody, binding portion, probe or ligand has to bind to the external vestibule portion to inhibit transport so as to allow the metes and bounds of the claim to be determined. Also it is not clear what is the "binding portion" a portion of? What is considered a probe, and what it a probe for. Further it is not clear how the ion channel is provided

so as to allow the metes and bounds of the claim to be determined. It is also not clear how the antibody, binding portion, probe or ligand that binds to the external vestibule portion is identified.

Claim 1 is indefinite because the preamble recites "A method of identifying an ion channel blocker for an ion channel" but the claim does not state how the goal of the preamble is achieved. An acceptable method claim must contain three sections: 1) a preamble, 2) method steps that clearly define what is to be done in each step, and 3) a conclusion that what was stated in the preamble was achieved.

Claims 5 and 23 is indefinite because it is unclear what is an "excitable cell". An "excitable cell" has not been defined in the specification or claims so as to allow the metes and bounds of the claim to be determined. Since cells respond to some kind of stimulus they can all be considered excitable.

Claims 6 and 24 are indefinite because it is unclear what is a "Kv ion channel". A "Kv ion channel" has not been defined in the specification or claims so as to allow the metes and bounds of the claim to be determined.

Claims 8 and 26 are indefinite because it is unclear what is the definition of "K1.2, Kv1.3 or Kv3.1" ion channels and how they are differentiated from each other and from other ion channels so as to allow the metes and bounds of the claim to be determined. "K1.2, Kv1.3 or Kv3.1" have not been defined in the specification or claims so as to allow the metes and bounds of the claim to be determined.

Claim 19 is indefinite because it is unclear what is being evaluated in/on the cell to determine if an ion channel blocker binds to the external vestibule so as to allow the metes and bounds of the claim to be determined. Claim 19 is also indefinite because the preamble recites "A method for screening a drug for effectiveness as an ion channel blocker for an ion channel" but the claim does not state how the goal of the preamble is achieved. An acceptable method claim must contain three sections: 1) a preamble, 2) method steps that clearly define what is to be done in each step, and 3) a conclusion that what was stated in the preamble was achieved.

Claim 20 is indefinite because it is not clear if the antibody, binding portion, probe or ligand has to bind to the external vestibule portion to inhibit transport so as to allow the metes and bounds of the claim to be determined. Also it is not clear what is the "binding portion" a portion of? What is considered a probe, and what it a probe for. It is also not clear how the antibody, binding portion, probe or ligand that binds to the external vestibule portion is identified.

Claims 2, 3, 4, 7, 9, 21, 22, 25 and 27 are rejected for depending on an indefinite base or intermediate claim and fail to resolve the issues raised above.

Claim Rejections, 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled

the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claims 1-8 and 19-26 are rejected under 35 U.S.C. 102(e) as being anticipated by Chandy et al (Ref A). Chandy et al disclose a method of identifying an ion channel blocker for an ion channel (MK3) having an external vestibule portion, amino acids 371-385 of SEQ ID NO:2 which have 91.0% query match and 86.7% best local similarity to SEQ ID NO:4 of instant application. The ion channel was isolated from mouse T-lymphocytes (considered an excitable cell, absent evidence to the contrary), expressed in oocytes and investigated for response to different ion blocking drugs (Fig 3, and columns 12-17, claims 1-7). Further disclosed is the production and use of antibodies raised against potassium channels and using said antibodies as screening agents for their ability to affect potassium channels electrophysiology and their ability to destroy cells expressing potassium channels (column 10 and column 16, lines 24-46). The ion channels used Chandy et al are inherently Kv ion channels encompassing KvI.1, Kv1.3 or Kv3.1, absent evidence to the contrary. Therefore, the disclosure of Candy et al of a method of identifying an ion channel blocker for an ion channel meets the limitations of claims 1-8 and 19-26, absent evidence to the contrary.

5. Claims 1-2 and 19-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Kem at al (Ref B). Kem et al disclose a method of identifying an ion channel blocker for an ion channel (Kv1.3) having an external vestibule portion. Kem et al have used methods to determine the selectivity of potassium channel blockers on a variety of potassium channels, wherein the blockers target the external vestibule.

Disclosed are:

a) "The restricted tissue distribution of Kv1.3 and its immunosuppressive action upon T-cells has prompted several pharmaceutical companies to attempt development of specific Kv1.3 blockers for therapeutic use as immunosuppressants" (column 2, lines 4-10)

b) "the external loop between S5 and S6 contains at least part of the dendrotoxin receptor", (dendrotoxins are K channel toxins isolated from sea anemone), "this region contains over 40 residues of sequence, and about half of these contribute towards pore formation" (column 2, lines 20-39). Further, "A short stretch of amino acids, the P-region, located between the fifth and sixth transmembrane segments, contributes to the formation of the channel pore. Delineation of the spatial organization of the residues in the P-region would help define the structure of ion channel conduction pathway and be valuable for understanding the mechanism of ion permeation", (column 3, second paragraph).

c) ""scorpion K channel toxins (charbdoxtoxin as protype) are potent blockers of KvI.1, Kv1.2 or 1.3 Shaker type DR channels", (column 2, lines 39-44).

d) K channel blockers are useful "as "molecular calipers" for measuring distances between K channel amino acid residues in the outer vestibule of these channels", (column 2, lines 44-50). Further disclosed is now that the structure of ShK toxin is known it will be possible to design additional analogues to define the full extent of the binding surface and to undertake complementary mutagenesis on the Kv1.3 channel to define the interacting residues on the channel (column 41, paragraph 2). Also disclosed, "Mutations in the P-region dramatically alter ShK blocking affinities,

consistent with the toxins interaction with residues in the external vestibule", (column 58, lines 52-57). In addition, "A computer model of the toxin-binding site of Kv1.3 is being used to conceptualize toxin docking to the vestibule (column 59, paragraph 1). Further stated is, "Owing to their unique structure and high affinity for at least some potassium channels, ShK toxin and related sea anemone potassium channel toxins may be useful molecular probes for investigating potassium channels" (column 42, paragraphs 1 and 2). "Eighteen synthetic analogs of ShK toxin were prepared in order to identify functionally important residue", (column 49, paragraph 3). Figure 15 shows ShK toxin behaved as a channel blocker. Column 69, last paragraph discloses, "Compounds which show a degree of similarity to the ShK pharamacophore will be tested for K-channel binding. Any compounds found to have binding affinity will constitute valuable new leads, which could then be modified with the aim of improving binding affinity and channel sub-type specificity". Also contemplated is the search for specific antagonists for potassium channel blocker (column 71, last paragraph).

e) Figure 6 and column 20 show a method for identifying an ion channel blocker specifically, "Inhibition of [^{125}I]-ChTX binding to rat brain membranes by natural and synthetic ShK toxin". Figure 7 and column 20 show a method for identifying an ion channel blocker for Kv1.3, specifically disclosed is "Inhibition of [^{125}I]-ChTX binding to Kv1.3 channels by ShK toxin". Figure 15 shows block of Kv1.3 current by ShK toxin, Figure 17 shows binding of ShK toxin analog, Figure 23, shows binding of ShK toxin to K channels (Kv1.1, Kv1.2 or Kv1.3, Kv1.5, Kv3.1) and membrane potential data, Figure 24 shows comparative data for ShK and ShK, K22DAP binding affinity for K

channel Kv1.3, Figure 25 shows comparative binding data for ShK toxin and ShK, K22DAP for Kv1.1. ChTx is charybdotoxin and ShK is a novel toxin isolated from sea anemone *Stichodactyla helianthus*, both toxins "interact strongly with the P-region"(column 3, second paragraph). The "P-region" disclosed by Kem et al is analogue to the "external vestibule" claimed in instant invention.

f) The expression of Kv1.3 potassium channels is detected in T-cells, brain, B-lymphocytes, microglia, macrophages, osteoclasts and platelets (column 25, second paragraph).

g) The inventors have searched for other novel peptides that might be truly selective for Kv1.3 and assessed the selectivity on a panel of cloned Kv channels. Also screened were cloned channels to identify Kv1.3-selective antagonist (column 25, lines 16-35, Table 8 and Example 13).

h) Ion channel toxin 3D structure and channel-binding surfaces were used to provide information which was used as the basis for design of smaller peptidic analogues of toxin, and eventually of peptidomimetic analogs (column 25, lines 36-53). Also disclosed are the production of analogs of ShK which have a higher half life (column 26, paragraph 5). Further compounds showing a degree of similarity to the ShK pharamacophore are tested for K-channel binding, and those having binding affinity constitute valuable new leads, which may be further modified with the aim of improving binding affinity and channel sub-type specificity (column 28, paragraph 4).

The ion channels used Kem et al are inherently Kv ion channels encompassing KvI.1, Kv1.3 or Kv3.1, absent evidence to the contrary. Therefore, the disclosure of Kem et al of a method of identifying an ion channel blocker for an ion channel meets the limitations of claims 1-2 and 19-24, absent evidence to the contrary.

6. Claims 1-2 and 19-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Stuhmer et al (Ref C).

Stuhmer et al disclose isolation of a family potassium channels (RCK 1, RCK 3, RCK 4 and RCK 5) from rat cortex and characterization of the channels expressed in Xenopus laevis oocytes following microinjection RCK-specific RNAs (see Abstract and Results). Also disclosed are transmembrane segments, S1 to S6, and the external vestibule portion, amino acids 356-360 of RCK 4 and RCK 5 (Fig. 2), are 100% identical to SEQ ID NO:1 of instant application . A profile of the pharmacological sensitivity of different RCK channels to K channel blockers 4-aminopyridine (4-AP) and tetraethylammonium (TEA) and several basic toxins was determined (Table 4). The results suggest that the reduced DTX sensitivity of Shaker, RCK3 and RCK4 channels may be due to a replacement of Asp 354 of RCK 5 in the S5-S6 bend region (external vestibule portion) by uncharged amino acids page 3242, column 1, last paragraph). Further, Stuhmer et al suggest, "To establish the molecular identity of a K^+ channel in its native cell membrane and a particular RCK channel expressed in Xenopus oocytes, properties such as the voltage and the time dependence, the single-channel amplitude and the susceptibility to blockers should be compared", (page 3240, column 2, Discussion). The ion channels used Stuhmer et al are inherently Kv ion channels, absent evidence to the contrary. Therefore, the disclosure of Stuhmer et al of a method of identifying an ion channel blocker for an ion channel meets the limitations of claims 1-2 and 19-24, absent evidence to the contrary.

Claim Rejections, 35 U.S.C. 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 and 19-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kem et al. (Ref.B) in view of Chandy et al (A) and further in view of Chandy et al (D), Stuhmer et al (C), Yatani et al (see IDS), Vassiliv et al (see IDS), Tejedor et al (E).

Kem et al disclose a method of identifying an ion channel blockers for an ion channel having an external vestibule portion. Kem et al have used methods to determine the selectivity of potassium channel blockers on a variety of potassium channels, wherein the blockers target the external vestibule. A detailed description of the disclosure of Kem et al is provided in "Claim Rejections, 35 U.S.C. 102", above. Kem et do not disclose: a) use of antibody as an ion channel blocker; and b) wherein the external vestibule portion has a sequence corresponding to SEQ ID NO:1, SEQ ID NO:3 or SEQ ID NO:4.

Chandy et al (Ref A) disclose a method of identifying an ion channel blocker for an ion channel (MK3) having an external vestibule portion, amino acids 371-385 of SEQ ID NO:2 which

have 91.0% query match and 86.7% best local similarity to SEQ ID NO:4 of instant application. Further disclosed is the production and use of antibodies raised against potassium channels and using said antibodies as screening agents for their ability to affect potassium channels electrophysiology and their ability to destroy cells expressing potassium channels (column 10 and column 16, lines 24-46). A detailed description of the disclosure of Candy et al is provided in "Claim Rejections, 35 U.S.C. 102", above.

Chandy et al (D) disclose a family of three mouse potassium channel genes (MK1, Mk2 and MK3) with intronless coding regions (see abstract). Also disclosed are transmembrane segments, S1 to S6, and the external vestibule portion, amino acids 374-388 of MK2 is 100% identical to SEQ ID NO:1 of instant application .

Stuhmer et al disclose isolation of a family potassium channels (RCK 1, RCK 3, RCK 4 and RCK 5) from rat cortex and characterization of the channels expressed in Xenopus laevis oocytes following microinjection RCK-specific RNAs (see Abstract and Results). Also disclosed are transmembrane segments, S1 to S6, and the external vestibule portion, amino acids 356-360 of RCK 4 and RCK 5 (Fig. 2), are 100% identical to SEQ ID NO:1 of instant application . A profile of the pharmacological sensitivity of different RCK channels to K channel blockers 4-aminopyridine (4-AP) and tetraethylammonium (TEA) and several basic toxins was determined (Table 4). The results suggest that the reduced DTX sensitivity of Shaker, RCK3 and RCK4 channels may be due to a replacement of Asp 354 of RCK 5 in the S5-S6 bend region (external vestibule portion) by uncharged amino acids page 3242, column 1, last paragraph). Further, Stuhmer et al suggest, "To

establish the molecular identity of a K^+ channel in its native cell membrane and a particular RCK channel expressed in Xenopus oocytes, properties such as the voltage and the time dependence, the single-channel amplitude and the susceptibility to blockers should be compared", (page 3240, column 2, Discussion)

Yatani et al disclose a monoclonal antibody (mAb) to α subunit of Gk blocks muscarine activation of atrial K^+ channels (see abstract). Inclusion of mAb 4A blocked carbachol activation of channel currents (page 829, column 1, last paragraph).

Vassiliv et al disclose the use of antibodies against conserved segments of the sodium channel α subunit slow the inactivation of sodium channels in rat muscle cells (Abstract). The specificity of the antibody-induced modification of N^+ currents was tested by using peptides to block the immunoreactivity of the antibody (Fig 2A). Further disclosed are: a) N^+ channels bind scorpion toxins and sea anemone toxins, which act at an extracellular site and specifically slow N^+ channel activation (page 1659, column 3, last paragraph); and b) "results indicate that the process of N^+ channel inactivation can be modified from the extracellular surface of the molecule by antibodies as well as by polypeptide neurotoxins from scorpion sea anemone, coral, and snail" (page 1161, column 1, first paragraph).

Tejedor et al disclose the use of antibodies raised against the "external vestibule portion" of the α subunit of sodium channel in determining α-scorpion toxin modification of sodium channel. Tejedor et al state, "The α-scorpion toxins modify sodium channel properties from the extracellular surface of the channel", and, "Therefore , our results provide direct evidence that at least a portion

of the segment of α subunit located between amino acid residues 355 and 378 is extracellular as illustrated in Fig. 2". It is proposed that a portion for α-scorpion toxin is formed by peptide segment(s) between amino acid residues 355 and 378 which is located in an extracellular loop between transmembrane helices S5 and S6 of homologous domain I of the sodium channel α subunit (Abstract), i.e. "external vestibule portion".

The references above disclose: a) Assays for screening or methods of identifying ion channel blockers are known in the art; b) "external vestibule portion" of channel proteins is known in the art and has been used in methods to identify and screen ion channel blockers; c) antibodies are routinely used to screen ion channel function and d) antibodies to "external vestibule portion" of ion channels are known in the art .

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use the method of identifying ion channel blockers or method for screening a drug as an ion channel blocker, wherein the ion channel has an "external vestibule portion", by contacting a cell having an ion channel with an ion channel blocker candidate, and evaluating the cell to determine if the ion channel blocker binds to the external vestibule portion of the ion channel and inhibits ion channel transport through the ion channel by using the method of Kem et al or Chandy et al., by incorporating the ion channel comprising polypeptide of SEQ ID NO:1, as disclosed by Stuhmer et al or Chandy et al (Science) , for delineation of the spatial organization of the residues in the "external vestibule portion" to define the structure of ion channel conduction pathway and understanding the mechanism of ion permeation or screening for ion channel blockers wherein the

ion channel blocker is an antibody as disclosed by Yatani et or Vassiliv et al. , or a ligand as disclosed by Kem et al. The ordinary artisan would have been motivated to use the method of Kem et al or Chandy et incorporating the ion channel "external vestibule portion" comprising SEQ ID NO:1, as disclosed by Stuhmer et al or Candy et al (Science), and use ion channel blockers which are ligands or antibodies in said method because Kem et al disclose "Mutations in the P-region dramatically alter ShK blocking affinities, consistent with the toxins interaction with residues in the external vestibule", (column 58, lines 52-57) and K channel blockers are useful "as "molecular calipers" for measuring distances between K channel amino acid residues in the outer vestibule of these channels", (column 2, lines 44-50). Further, the ordinary artisan would have been motivated use antibody as ion channel blockers because antibodies are known in the art for the "external vestibule portion" of the ion channels, or can be easily produced from known "external vestibule portion" of ion channels by standard methods in the art, and further said antibodies are routinely used in the methods disclosed above as shown by Chandy et al, Tejedor et al, Yatani et al and Vassiliv et al.

The ordinary artisan would have expected success at using the above mentioned method for method of identifying ion channel blockers or method for screening a drug as an ion channel blocker, wherein the ion channel has an "external vestibule portion", because Kem et al, as well as others , have shown the importance of the "external vestibule portion" of an ion channel a key target for compounds showing a degree of similarity to the ShK pharamacophore and said compounds can be tested for K-channel binding, and those having binding affinity constitute valuable new leads, which may be further modified with the aim of improving binding affinity and channel sub-type specificity

(column 28, paragraph 4). Further, since antibodies can be specifically targeted to the "external vestibule portion" of ion channels, they too would constitute as compounds that could be tested for K-channel binding, the specificity of the antibody-induced modification of ion currents can be tested by using peptides to block the immunoreactivity of the antibody, as is the case for antibody-induced modification of N^+ currents disclosed by Vassiliv et al.

No claim is allowed.

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
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Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal Basi whose telephone number is (703) 308-9435. The examiner can normally be reached on Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nirmal S. Basi
Art Unit 1646
March 12, 2001